

Liver Disease in Women: The Influence of Gender on Epidemiology, Natural History, and Patient Outcomes

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Abstract: Women more commonly present with acute liver failure, autoimmune hepatitis, benign liver lesions, primary biliary cirrhosis, and toxin-mediated hepatotoxicity. Women less commonly have malignant liver tumors, primary sclerosing cholangitis, and viral hepatitis. There is a decreased rate of decompensated cirrhosis in women with hepatitis C virus infection, no survival difference in alcohol-related liver disease, and improved survival from hepatocellular carcinoma. In general, men are 2-fold more likely to die from chronic liver disease and cirrhosis than are women. Liver transplant occurs less commonly in women than in men, with variable disease outcomes based on etiology. This review highlights the epidemiology, natural history, treatment outcomes, and pathophysiology of common liver diseases in women and discusses how gender influences disease incidence, presentation, progression, and outcomes. Pregnancy-related liver disease is not covered.

The pathophysiology of gender differences in the incidence, natural history, and outcomes of common liver diseases is incompletely understood. Various potential mechanisms include the effect of sex hormones on oxidative and metabolic pathways, differential gene transcription in response to injury in women compared with men, and sex differences in immune regulation. In addition, differences in access to care and treatment, as well as diagnostic considerations, may affect gender differences in liver disease.

Alcohol and Toxic Liver Injury

Women are more commonly affected by toxin-mediated liver disease, such as alcohol- and drug-induced liver disease, and have an increased prevalence of acute liver failure.¹⁻³ Women are more susceptible than men to the toxic effects of alcohol on the liver for any given dose of alcohol, even though men abuse or depend on alcohol more than women, at a ratio of 2:1 in persons over the age of 26 years. A 12-year prospective study of alcohol use in over 13,000

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Table 1. Alcohol Consumption and Relative Risk of Death¹

	1 drink/day	2 to 3 drinks/day	4 or more drinks/day
Women	1.5 (95% CI, 0.8-2.8)	2.1 (95% CI, 1.3-3.4)	4.8 (95% CI, 2.9-7.9)
Men	1.2 (95% CI, 0.7-2.2)	2.6 (95% CI, 1.6-4.0)	7.5 (95% CI, 4.9-11.4)

participants in Denmark showed that the risk of development of alcohol-related liver disease increased in women who consumed 7 to 13 beverages per week (84-156 g) compared with men who consumed 14 to 27 beverages per week (168-324 g; Table 1).¹ Among persons who consumed 28 to 41 beverages per week (336-492 g), the relative risk of alcohol-induced cirrhosis was 7.0 (95% CI, 3.8-12.8) in men vs 17.0 (95% CI, 6.8-40.8) in women. However, alcoholic cirrhosis is less frequently diagnosed in women, as shown in a population-based registry of 8482 Danish patients from 1993 to 2005 in which only 33% of patients were women.⁴

Compared with their male counterparts, women with alcoholic liver disease have a more rapid progression to fibrosis that persists even after abstinence from alcohol.^{5,6} Dietary factors are known to influence development of alcoholic liver disease. An analysis of 107,000 women from the United Kingdom suggests that the combination of high body mass index (BMI) and high alcohol intake increases the development of chronic liver disease.⁷ Whether there is a survival difference between the sexes regarding alcoholic liver disease is less clear. In a prospective study of 490,000 men and women in the United States who were followed for 9 years, the relative risk of death from cirrhosis or alcoholism was equal in both sexes for those consuming 2 to 3 drinks per day but was increased in men who consumed 4 or more drinks per day.⁸

Several factors likely contribute to the severity of alcoholic liver disease in women. Experiments in rats suggest that higher endotoxin levels and increased gut permeability to endotoxin likely contribute to more severe liver injury in females.^{9,10} Estrogen receptor concentrations within the liver differ between the sexes, and estrogen appears to activate liver Kupffer cells.¹¹ This results in increased inflammation and necrosis, which can be counteracted by treating female rats with an antiestrogen.¹² Alcohol also may induce differential expression of genes in rats, leading to increased oxidative stress, inflammation, and injury in female rats.¹³

Women are more likely to present with drug-induced hepatotoxicity and acute liver failure than are men. Prospective data from the Acute Liver Failure Study Group, which included 23 sites from 1998 to 2007, showed that 67% of the 1147 patients were women.² Among 133 cases of drug-induced liver injury assessed, 71% were

in women, and women accounted for over 70% of all patients hospitalized with acute liver injury due to acetaminophen and idiosyncratic drug reactions. However, gender is not a predictor of survival in acute liver failure.³

The female preponderance of drug-induced liver injury may, in part, be related to sex differences in drug bioavailability, metabolism, and excretion, which have been well described in rat and mouse models as well as in humans.¹⁴ There are multiple variations in expression of cytochrome p450 enzymes, which results in varying susceptibility to drugs. Women, for example, are more likely to express CYP3A4, an important mediator of liver oxidative metabolism and a key enzyme in most drug metabolism.¹⁵

Autoimmune Liver Diseases

Women are 10 times more likely to have primary biliary cirrhosis (PBC) than men and 4 times as likely to have autoimmune hepatitis.^{16,17} The exact mechanism of gender differences in autoimmune liver disease and autoimmunity in general is not known; however, both immunogenetics and sex hormones play a complex and, perhaps, interactive role. Sex steroids alter the immune system on many levels: they can regulate gene expression through steroid-responsive elements, alter antigen presentation through effects on human leukocyte antigen genes, and alter the cytokine environment.^{18,19} Additionally, X chromosome monosomy and fetal microchimerism (the presence of fetal cells in maternal circulation) may play a role in the pathogenesis of PBC.^{20,21} In the case of PBC, epidemiologic studies also have shown different environmental risk factors between sexes, including hair dye use, recurrent urinary tract infections, smoking, and estrogen deficiency, all of which may contribute to increased disease in women.²²⁻²⁴ In patients with PBC, overall survival is similar between both sexes.²⁵ Women with PBC present at a younger age with increased rates of pruritus and appear to have slower rates of fibrosis than men.^{6,26} In patients with autoimmune hepatitis, the rates of progression to cirrhosis, treatment failure, and death from liver failure were equivalent in men and women.²⁷

Women are less likely to have primary sclerosing cholangitis (PSC). In a study of residents from Olmsted County, Minnesota, the incidence of PSC was 1.25 per 100,000 person-years (95% CI, 0.70-2.06) in men and

0.54 per 100,000 person-years (95% CI, 0.22-1.12) in women.²⁸ Over 60% of patients with PSC are male.²⁹ Gender is not an independent risk factor for mortality in PSC, although one study found that cholangiocarcinoma was more common in men.³⁰⁻³²

Liver Tumors

There are gender differences in the incidence of both benign and malignant liver tumors (Table 2). Whereas the majority of benign liver tumors are more common in women, malignant tumors are more common in men.

Benign liver lesions that predominantly occur in women include cavernous hemangioma, focal nodular hyperplasia (FNH), hepatic adenoma, biliary cystadenoma, and solitary hepatic cysts. Hemangioma has the highest prevalence at 1.4%, while FNH has a prevalence of 0.4% to 3% and adenoma has a prevalence of 0.003%.³³ The prevalence of simple hepatic cysts is 0.1% to 2.5%, but imaging recognition increases with age.³⁴ Biliary cystadenoma and adenocarcinoma are rare (1% of cystic liver lesions), and women account for 96% of cystadenomas and 66% of cystadenocarcinomas.³⁵ Simple hepatic adenomas are monoclonal tumors that are defined as hepatocyte nuclear factor 1- (HNF1A)-inactivated adenomas (30%-40%), inflammatory adenomas (35%), and, less frequently, beta-catenin-activated adenomas (15%-19% of large series).³⁶ The first 2 types of adenomas are more common in women, and men are more predisposed to beta-catenin-activated adenomas. Beta-catenin-activated adenomas have a higher risk of malignant transformation.³⁷ The data are less convincing regarding whether a gender discrepancy exists in nodular regenerative hyperplasia.³⁸

Estrogen levels are thought to be associated with benign liver tumors, although the potential mechanisms are unclear. The data are inconsistent in determining whether there are increased hormone receptors on benign tumors and whether exogenous estrogens, such as oral contraceptive pills (OCPs), stimulate benign tumor growth. The evidence regarding OCP influence on benign liver lesions is most compelling for adenomas, with 80% of women reporting OCP use.³⁷ Therefore, discontinuation of OCPs is recommended for such patients. For other liver lesions, there is less convincing evidence for the role of OCPs on tumor progression. A small case-control study suggested that patients taking OCPs were at increased risk of FNH.³⁹ However, a study of 136 women followed for 9 years did not show an association in size or number of FNH lesions in OCP users.⁴⁰ The overall survey of literature suggests no increased risk of FNH or change in character of FNH on OCPs, and discontinuation is not recommended in these patients. Likewise, there

Table 2. Female-to-Male Ratio of Benign and Malignant Hepatic Tumors

	Female-to-Male Ratio	Overall Prevalence ^a
More Common in Women		
Cavernous hemangioma	5-6:1	1.4% ³³
Focal nodular hyperplasia	6-8:1	0.4%-3% ³⁶
Adenoma – <i>HNF1</i> -inactivated – Inflammatory	>8-9:1	3 per 100,000 persons on OCP
Hepatic cyst	4:1	0.1%-2.5% ³⁴
Biliary cystadenoma	25:1	1% of liver cysts ³⁵
Biliary cystadenocarcinoma	2:1	
Less Common in Women		
Beta-catenin-activated adenoma	1:4	
Hepatocellular carcinoma	1:3-4	

^aOverall prevalence, not by gender.

OCP, oral contraceptive pill.

is debate over whether estrogen use increases rates of cavernous hemangiomas. In a study of 94 women followed from 1986 to 2003 (mean follow-up of 7 years), there was a trend toward an increased incidence of cavernous hemangiomas and hormone therapy, but this trend was not statistically significant.⁴¹

In benign liver lesions, an emerging understanding of the molecular pathogenesis of FNH and adenomas suggests that men are predisposed to the subset of adenomas characterized by beta-catenin activation, whereas women appear to have an inactivating mutation of a gene involved in estrogen metabolism (CYP1B1), which results in an increased risk of the HNF1A subtype of adenomas.⁴² Inflammatory adenomas activate JAK-STAT signaling, which results in inflammation. *HNF1* is a human tumor suppressor gene, and one study found inactivating mutations of *HNF1* in 35% to 50% of hepatic adenomas.³⁶ Inactivating mutations of the *HNF1* gene were noted in a small minority of cases of well-differentiated hepatocellular carcinomas (HCCs), particularly in cases of HCC that developed in the absence of cirrhosis.

HCC is the most common primary malignant tumor of the liver and affects men 3 to 4 times more frequently than women.⁴³ HCC is the fifth most common malignancy in men and the ninth most common in women.⁴⁴ Data from the Surveillance, Epidemiology, and End Results (SEER) cancer statistics database showed that the annual incidence rate for men was 6.7 per 100,000 years compared with 2.0 per 100,000 years for women. Interestingly, the peak incidence in women occurs 2 decades

later than that in men (4.4 per 100,000 years at age 65 to 69 years vs 4.2 per 100,000 years at age 45 to 49 years, respectively). The ratio of male to female cancer cases was similar across all racial and ethnic groups.⁴⁵ The gender difference in HCC incidence persists after adjusting for increased rates of confounding diagnoses, such as viral and alcoholic hepatitis, which are more common in men. A retrospective analysis of a US cancer database involving over 7000 patients from 1977 to 1996 showed that women and men had the same 1-year HCC survival rate of 23% (95% CI, 21%-24%) during 1992 to 1996.⁴⁶ An analysis of the SEER database from 1998 to 2001 showed that 3-year survival was similar in men and women for surgical resection, transplant, and radiofrequency ablation.⁴⁷ Management of liver cancer does not differ significantly between the sexes; however, there are differences in surveillance recommendations (eg, the American Association for the Study of Liver Diseases guidelines recommend HCC surveillance starting at age 50 years in Asian women compared with age 40 years in Asian men).⁴⁸

The pathophysiology underlying the sex differences in HCC and benign liver lesions continues to be elucidated. There is evidence that HCC is an androgen-sensitive tumor and that sex hormones promote tumor proliferation.^{49,50} For example, one study showed that estrogen decreased the secretion of interleukin-6 from liver Kupffer cells in mice, resulting in less cancer.⁵¹

Nonalcoholic Fatty Liver Disease

There are conflicting data on gender in nonalcoholic fatty liver disease (NAFLD), which represents a spectrum of histologic manifestations, including steatosis, steatohepatitis, and cirrhosis. Some studies found that women were less commonly affected by NAFLD.^{52,53} NAFLD is most frequently recognized in men and postmenopausal women who have not received hormone replacement therapy (HRT).⁵⁴ This suggests that sex hormones, particularly estrogen, play a role in the pathogenesis of NAFLD.⁵⁵ In a population-based cross-sectional study, Liu and colleagues studied 4338 women aged 20 to 60 years who were enrolled in the Third National Health and Nutrition Examination Survey from 1988 to 1994.⁵⁶ The researchers found that current OCP users showed a 50% lower odds of NAFLD than never users (adjusted odds ratio, 0.50; 95% CI, 0.26-0.98) after adjusting for age, race/ethnicity, smoking status, history of diabetes or hypertension, and education. When the researchers adjusted for BMI or waist circumference, the relationship was attenuated. However, among 1266 patients in the US nonalcoholic steatohepatitis (NASH) network, 64% were female, and those with NASH were more likely to be female and to have diabetes and metabolic syndrome. These data may be explained

by true increased prevalence, older age of participants, or different interest between men and women in pursuing healthcare and participating in studies.⁵⁷

Viral Hepatitis

Women clear acute hepatitis C virus (HCV) infection at a higher rate than do men.⁵⁸ Of Irish women who were recipients of HCV-contaminated anti-D immune globulin in 1977 to 1978, only 55% were found to be viremic 17 years later.⁵⁸ In addition, progression to severe liver disease was less common than that reported in men.^{58,59} In this same cohort, although inflammation was common 20 years after infection, it was minimal (41%) or moderate (52%) in nearly all patients. Although biopsy samples from 186 of the 363 (51%) women showed evidence of fibrosis, only 7 (2%) women had probable or definite cirrhosis, and 2 of these 7 reported excessive alcohol consumption. After 3 decades, only 27% showed progression of liver fibrosis, and cirrhosis developed in only 4 (2.1%) women.⁶⁰

There is very little information available on the progression of liver disease in women after menopause; a single cross-sectional study of 251 women demonstrated increased progression after menopause in HCV mono-infected women.⁶¹ There are no large studies of the progression of HCV infection through the menopausal transition.

In contrast to the hypothesis that estrogen potentiates fibrosis in alcoholic liver disease, estrogen may have a protective role against fibrosis in viral hepatitis by inhibiting stellate cells, which are responsible for fibrogenesis in the liver.⁶² Animal studies in rats suggest that estradiol decreases fibrosis progression.⁶³ In addition to menopause, comorbid factors have been shown to increase fibrosis progression, such as a higher BMI, metabolic syndrome, and steatosis.⁶⁰ In a study of 251 women in which 121 were postmenopausal and 65 were receiving HRT, menopausal women receiving HRT had a lower-stage fibrosis.⁶¹ HCV-infected women have a better response to interferon- and ribavirin-based therapies in some studies but not others.^{64,65} Early menopause has been reported to decrease response to therapy.⁶⁶ These sex differences are unlikely to be seen with all oral direct-acting antiviral agents.

Hepatitis B virus (HBV) affects men and women similarly. However, male sex is a risk factor for reactivation of HBV infection after seroconversion from hepatitis B e antigen–positive to –negative and for the development of cirrhosis and HCC.⁶⁷

Metabolic Liver Disease

There are limited data on gender differences in Wilson disease. In a cohort study of 627 consecutive patients

Table 3. The Incidence and Outcome of Common Liver Diseases in Women Compared with Men

Disease	Relative Incidence Female:Male	Outcome in Women
Increased Incidence		
Autoimmune hepatitis	4:1 ¹⁷	No survival difference ²⁷
Benign liver lesions	See Table 2	NA
Drug-induced liver injury	2:1 ²	No survival difference ³
Primary biliary cirrhosis	10:1 ¹⁶	No survival difference ²⁵
Decreased Incidence		
Alcohol-related liver disease	2:1 ⁴	More severe ¹
Beta-catenin-activated adenoma	See Table 2	NA
Hepatocellular carcinoma	See Table 2	No survival difference
Primary sclerosing cholangitis	1:2.3 ²⁸	No survival difference ²⁹
Similar Incidence or Conflicting Data		
Hepatitis B virus infection		Less severe ⁶⁷
Hepatitis C virus infection		Less severe ⁶⁰
Metabolic liver disease		Hemochromatosis less severe in women ⁷⁰
Nonalcoholic fatty liver disease		Women more likely to have diabetes and metabolic syndrome ⁵⁷

NA, not available.

with Wilson disease in Poland, women were less likely to be affected by the disease overall than men (47% vs 53%).⁶⁸ However, women were more likely than men to present with the hepatic form than the neuropsychiatric form (58% vs 42%, respectively). There does not appear to be a gender difference in the incidence of genetic hemochromatosis⁶⁹; however, men have higher ferritin and transferrin saturation levels than do women, including in those with genetic hemochromatosis and in those without.⁷⁰ The disease phenotype of C282Y hereditary hemochromatosis differs between the sexes, with 28% of men showing symptomatic iron overload, compared with 1% of women.⁷¹ In murine models, sex differences exist in the levels of hepcidin expression, an important mediator of iron balance.⁷² Whether this translates to human iron overload requires further exploration.

Cirrhosis and Liver Transplantation

In general, men are 2-fold more likely to die from chronic liver disease and cirrhosis than are women, according to an analysis by the National Center for Health Statistics that was reported in 2005.⁷³ Women represent approximately 30% of liver transplant recipients.⁷⁴ Women appear more likely than men to die on the waiting list in the Model for End-Stage Liver Disease (MELD) era vs the pre-MELD era.⁷⁵ In fact, the disparity in transplant rates for women has increased in the MELD era as waiting-list mortality risk has risen, in particular for MELD scores of

15 or greater.⁷⁶ In one study, female sex predicted wait-list mortality as did fulminant hepatic failure, primary nonfunction, blood group O recipients, and advanced liver disease (MELD score 20 or greater).⁷⁷ Whether the increased mortality for women is associated with lower creatinine levels and, thus, lower MELD scores is unclear. A study of United Network for Organ Sharing (UNOS) data in the MELD era showed that women have a 19% higher wait-list mortality than do men. This is, in part, explained by size differences between men and women, as correcting for height explained the mortality difference in one multivariate analysis.⁷⁸ Organ Procurement and Transplantation Network/UNOS data confirm that women have better long-term survival after liver transplant than do men. However older age (>65 years) is associated with worse outcomes, and older donors (>60 years) are more likely to be female.⁷⁹

The natural history of liver disease in women varies according to etiology. Although women have slower progression of fibrosis and decreased incidence of cirrhosis pretransplantation,^{59,80} after liver transplantation, women have a higher risk of advanced fibrosis and graft loss in HCV-related disease.^{81,82} In the most recent investigation of the role of sex and transplant outcomes in HCV-related disease, women had a 31% increased risk of advanced recurrent disease compared with men in multivariate models.⁸² In patients transplanted for HCV-related disease, women have a 14% increased risk of death at 5 years compared with men.⁸³

Conclusion

Gender differences in incidence, presentation, natural history, and outcomes exist for common liver diseases (Table 3). These variations are important for the clinician to recognize, as they influence the likelihood of a given diagnosis for a patient and the potential for progression of the liver disease. This review highlights the most striking gender differences in incidence and natural history. Gender does not typically shape therapeutic decisions, although it does influence the incidence and natural history of many liver diseases. Further studies are required to assess the role of sex hormones as well as varying health behaviors and treatment preferences based on gender.

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